Long-term Glycemic Variability and Risk of Adverse Outcomes: A Systematic Review and Meta-analysis

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OBJECTIVE

Glycemic variability is emerging as a measure of glycemic control, which may be a reliable predictor of complications. This systematic review and meta-analysis evaluates the association between HbA_{1c} variability and micro- and macrovascular complications and mortality in type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Medline and Embase were searched (2004–2015) for studies describing associations between HbA_{1c} variability and adverse outcomes in patients with type 1 and type 2 diabetes. Data extraction was performed independently by two reviewers. Random-effects meta-analysis was performed with stratification according to the measure of HbA_{1c} variability, method of analysis, and diabetes type.

RESULTS

Seven studies evaluated HbA_{1c} variability among patients with type 1 diabetes and showed an association of HbA_{1c} variability with renal disease (risk ratio 1.56 [95% CI 1.08–2.25], two studies), cardiovascular events (1.98 [1.39–2.82]), and retinopathy (2.11 [1.54–2.89]). Thirteen studies evaluated HbA_{1c} variability among patients with type 2 diabetes. Higher HbA_{1c} variability was associated with higher risk of renal disease (1.34 [1.15–1.57], two studies), macrovascular events (1.21 [1.06–1.38]), ulceration/gangrene (1.50 [1.06–2.12]), cardiovascular disease (1.27 [1.15–1.40]), and mortality (1.34 [1.18–1.53]). Most studies were retrospective with lack of adjustment for potential confounders, and inconsistency existed in the definition of HbA_{1c} variability.

CONCLUSIONS

HbA_{1c} variability was positively associated with micro- and macrovascular complications and mortality independently of the HbA_{1c} level and might play a future role in clinical risk assessment.

Current management of type 1 and type 2 diabetes uses the average glycemia measure HbA_{1c} to monitor control. This rationale is based on trial and observational evidence that lowering HbA_{1c} reduces the risk of the micro- and macrovascular complications of diabetes (1–4). Whether an average glycemic measure is most appropriate to assess the risk for complications is currently under debate. For example, one analysis of the Diabetes Control and Complications Trial indicated higher rates of retinopathy in the conventional treatment group than in the

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META-ANALYSIS

intensive treatment group over time in patients with similar average HbA_{1c} values in the two groups (5), suggesting that additional factors other than mean HbA_{1c} may be responsible for this increased retinopathy risk (5–7). Glycemic variability is now emerging as a possible additional measure of glycemic control, which may be a better predictor of complications than average glycemic measures.

Glycemic variability relates to fluctuations in glycemia. Short-term glycemic variability refers to within- or between-day fluctuations in an individual and includes multiple methods of assessment. Long-term glycemic variability refers to fluctuations over several weeks or months and is most commonly assessed by HbA_{1c} variability. However, neither have a standardized method of measurement or definition (8). A recent meta-analysis concluded that HbA_{1c} variability, assessed by the SD, is associated with renal disease in type 1 and type 2 diabetes (9). However, no systematic reviews or meta-analyses have evaluated the relationship between long-term glycemic variability and other complications in diabetes, despite contradictory literature providing evidence in support (6,10–15) and against (16–20) such a relationship.

Long-term glycemic variability is important for several reasons. First, unlike short-term glycemic variability, long-term glycemic variability may predict complications in both type 1 and type 2 diabetes (6,10–15,21–29). Second, HbA_{1c} is routinely recorded in primary care for both types of diabetes, whereas measures of short-term variability are not (30,31). Finally, it could be a potentially modifiable risk factor. Through a systematic review and meta-analysis, we evaluated the evidence for the association of HbA_{1c} variability with mortality and complications in type 1 and type 2 diabetes to gain insight into the clinical utility of this relationship to predict adverse outcomes.

RESEARCH DESIGN AND METHODS

Data Sources and Searches

We searched Medline and Embase for articles published between 2004 and September 2014, using the search terms shown in the Supplementary Data. We updated the search in July 2015. C.S.K. conducted the initial search, and C.G. duplicated it. All resulting articles, including conference abstracts, were reviewed. Broad search criteria included diabetes terms, outcomes of interest terms, and exposure terms (HbA_{1c} variability).

Study Selection

We included studies of patients with diabetes that evaluated HbA_{1c} variability and adverse outcomes published within the past 10 years. No restrictions were placed on participant age or definition of HbA_{1c} variability used. The main adverse outcomes of interest were renal disease (diabetic nephropathy, microalbuminuria, macroalbuminuria, renal failure, chronic kidney disease), diabetic retinopathy, diabetic neuropathy, cardiovascular macrovascular events (myocardial infarction, ischemic heart disease, heart failure, stroke, peripheral vascular disease), and death. We excluded reviews, editorials, and case reports and searched the bibliographies of included studies and relevant reviews for additional studies. Study titles and abstracts were initially screened independently by two reviewers (C.G. and S.A.), and full articles on potentially relevant studies were downloaded and reviewed for inclusion. Five reviewers discussed and decided on the final inclusion of studies for this review and meta-analysis (C.G., C.S.K., S.A., E.K., M.A.M.) (Fig. 1).

Data Extraction and Quality Assessment

Data extraction was performed independently by two reviewers (C.G. and S.A.). Data collected were study design, participant characteristics, quality of study assessment, definitions of HbA_{1c} variability, outcomes evaluated, and results. Discrepancies in extractions were discussed with two other reviewers (C.S.K. and Y.L.).

Data Synthesis and Analysis

We conducted a random-effects meta-analysis of the adjusted risk estimates (where available) with use of the inverse variance method in RevMan 5.3 (Nordic Cochrane Centre). Analysis was stratified according to the definition of HbA_{1c} variability used, the method of analysis used, and the type of diabetes. In terms of HbA_{1c} variability, studies were divided into those that reported a coefficient of variation (CV) and those that reported an SD. Within the two groups, the analysis was further divided according to whether the highest variability group was compared with the lowest variability group or whether variability was measured per incremental increase in CV or SD. Where possible, we chose to analyze results for the group with the greatest HbA_{1c} variability against that of the one with lowest variability. If there were several groups with differing levels of variability, we conducted the meta-analysis based on the group with the greatest variability compared with the one with the least variability.

Both SD and CV are measures of variability. SD measures how much values differ from the group mean. CV is the ratio of SD to the mean, so it is a measure independent of the mean. The CV may be appropriate for parameters such as HbA_{1c} where the variability is likely to increase as the mean increases. However, there is no standardized method of measuring HbA_{1c} variability (8).

Where there were insufficient studies for pooling or significant heterogeneity that could not be explained, we performed narrative synthesis. We assumed similarity between risk ratios (RRs) and odds ratios (ORs) because adverse events are rare (32).

Statistical heterogeneity was assessed with the I^2 statistic (33), where values of 30–60% represent a moderate level of heterogeneity. Six sensitivity analyses were performed. These included prospective studies; studies with a follow-up of >5 years; and studies that adjusted for duration of diabetes, number of HbA_{1c} measurements, comorbidities, and baseline medications. Publication bias was assessed using funnel plots if there were >10 studies and no evidence of statistical heterogeneity in a particular meta-analysis (34).

RESULTS

Studies Included and Participant Characteristics

Figure 1 shows a flow diagram of the study selection process. Twenty studies in 87,641 participants met the inclusion criteria. Ten studies included participants from Europe (10,11,14,16–19,26,29, 35,36), eight from Asia (12,13,15,18,20,24, 27,28), four from North America (6,18,23, 25), and one from Australasia (18). The number of participants in each study

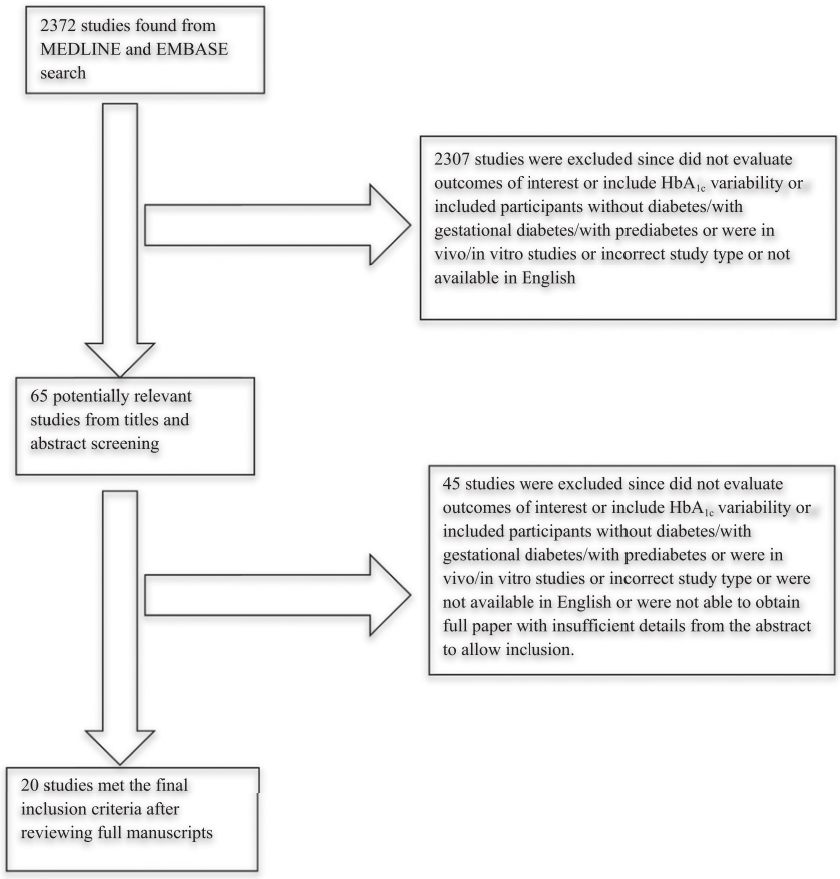

Figure 1—Flow diagram of study selection.

ranged from 234 to 35,891. Details of the study design and participants are shown in Table 1.

Type 1 Diabetes

Seven studies included 44,021 participants with type 1 diabetes (6,10,11,14,25,29,35). These comprised three retrospective cohort studies (11,14,25), two prospective cohort studies (10,29), one post hoc analysis of a randomized controlled trial (6), and one cross-sectional study (35). Most studies used data from secondary care apart from two (10,11) that used primary and secondary care data.

Type 2 Diabetes

Thirteen studies included 43,620 participants with type 2 diabetes (12,13,15–20,23,24,26–28,36). These comprised six retrospective cohort studies (13,15, 20,23,28,36), five prospective cohort studies (12,16,17,19,26,27), and two post hoc analyses of randomized controlled trials (18,24). All studies used secondary care data apart from one of primary and secondary care data (19) and one of solely U.S. primary care data (23).

Quality Assessment of Included Studies

The quality assessment of included studies is shown in Table 2. For both type 1 and type 2 diabetes, the outcome assessment varied from blood and urine tests for diabetic nephropathy, to fundoscopy for retinopathy, to formal follow-up for cardiovascular events and death. The frequency of outcome evaluation differed depending on the study. All studies adjusted for mean HbA_{1c}.

Type 1 Diabetes

The shortest follow-up was a mean of 5.2 years (11) and the longest, 23 years (14). The number of HbA_{1c} measurements per patient ranged from a median of 4 (29) to 13 (10). Data from all studies were unclear about loss to follow-up. All studies used some form of adjustment for baseline covariates; however, five did not adjust for baseline diabetes medications (10,11,14,25,29), and none adjusted for baseline hypertension medication.

Type 2 Diabetes

The shortest follow-up was 2 years (20) and the longest, a median of 15.9 years (13). The number of HbA_{1c} measurements per patient ranged from 3 (19) to a median of 79 (13). In six studies, loss to follow-up was unclear; six studies had $<$10% of participants lost to follow-up, whereas one had lost 27.5% to follow-up (13). All the studies used some form of adjustment for baseline covariates; however, six did not adjust for baseline diabetes medication (15,19,20,23,24,27), and four did not adjust for baseline hypertension medication (13,16,17,20, 27). Of the seven studies that did include hypertension medication (12,15,18, 23,24,26,28), two adjusted for ACE inhibitor/angiotensin receptor blocker use (23,24). The definition of glycemic variability, outcome evaluated, and study follow-up and results are shown in Table 3.

Adverse Outcomes

Type 1 Diabetes

Three studies evaluated adverse outcomes by considering the impact of HbA_{1c} CV (Supplementary Fig. 2) (11,14,35). There was no significant association between HbA_{1c} CV and retinopathy (RR [95% CI] 1.34 [0.89–2.04], two studies) or microalbuminuria (1.04 [1.00–1.08], one study). The study by Hermann et al. (14), however, reported that HbA_{1c} variability based on CV was associated with a 3.5% higher risk of diabetic retinopathy per 1-unit increase in HbA_{1c} CV at 10 years disease duration.

Four studies evaluated adverse outcomes associated with HbA_{1c} SD (Supplementary Fig. 2) (6,10,25,29). All showed a significant association of HbA_{1c} SD and adverse outcomes. Highest to lowest variation SD group was associated with an increased risk of nephropathy (RR [95% CI] 1.92 [1.49–2.47]) and cardiovascular events (1.98 [1.39–2.82]). Incremental increases in SD were also associated with increased risk of nephropathy (1.86 [1.41–2.46]), microalbuminuria (1.56 [1.08–2.25], two studies), and retinopathy (2.11 [1.54–2.89]).

No studies evaluated HbA_{1c} variability in type 1 diabetes and mortality. Sensitivity analyses for study type and studies

Table 1—Design and participant characteristics of studies that evaluated glycemic variability

Study ID	Study design; year; country	Sample size	Age	Male (%)	Inclusion criteria
Studies of participants with type 1 diabetes					
Hermann 2014 (14)	Retrospective cohort study; 1990–March 2013; Germany and Austria	35,891	Median 16 years	52	Participants in the German/Austrian Diabetes Prospective Documentation Initiative
Hietala 2013 (11)	Retrospective cohort study; 1997–January 2012; Finland	2,019	No prior laser treatment group: 35 years Proliferative diabetic retinopathy group: 39 years	49	Adult participants with type 1 diabetes who took part in FinnDiane
Kilpatrick 2008 (6)	Post hoc analysis of RCT; 1983–1993; U.S. and Canada	1,441	27 years	53	Participants in the Diabetes Control and Complications Trial data set
Marcovecchio 2011 (29)	Prospective cohort study; 1986–1996 and 2000–2005; U.K.	1,232	Median at diagnosis 9 years	55	Participants in the Oxford Regional Prospective Study, which included children with type 1 diabetes aged <16 years, and the Nephropathy Family Study, which included adolescents with type 1 diabetes aged 10–16 years
Nazim 2014 (35)	Cross-sectional study; 1985–2004; Poland	438	Mean at diagnosis 9 years	55	Children and adolescents with newly diagnosed type 1 diabetes under the care of the Endocrinology Department of University Children's Hospital
Raman 2011 (25)	Retrospective cohort study; 1993–2009; U.S.	893	Mean at diagnosis 8 years	47	Pediatric patients with type 1 diabetes in a single large tertiary care referral center
Wadén 2009 (10)	Prospective cohort study; November 1997–January 2009; Finland	2,107	36 years	53	Participants with type 1 diabetes diagnosed at age <35 years in FinnDiane, with insulin treatment initiated within 1 year of diagnosis
Studies of participants with type 2 diabetes					
Lin 2013 (28)	Retrospective cohort study; August 2002–August 2008; Taiwan	3,220	57 years	51	Participants with type 2 diabetes treated at the China Medical University Hospital
Cummings 2011 (23)	Retrospective cohort study; 1998–2008; U.S.	791	54 years	32	Participants with type 2 diabetes aged >18 years seen in one of the primary care practices (family medicine, internal medicine) in the southeastern U.S.
Foo 2014 (20)	Retrospective cohort study; not stated; Singapore	234	Not stated	Not stated	Participants attending a tertiary eye hospital in Singapore with serial HbA_{1c} monitoring for >2 years
Hirakawa 2014 (18)	Post hoc analysis of RCT; November 2001–2007; Asia, Australasia, Europe, North America	4,399	66 years	43	Participants >55 years of age with major macrovascular or microvascular disease or at least one vascular disease risk factor from 1 of 215 collaborating centers of the ADVANCE trial

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Table 1—Continued

Study ID	Study design; year; country	Sample size	Age	Male (%)	Inclusion criteria
Hsu 2012 (24)	Post hoc analysis of RCT; 2003–2010; Taiwan	821	At onset of diabetes 51 years	46	Participants with type 2 diabetes enrolled in the Diabetes Management Through an Integrated Delivery System project
Lang 2015 (36)	Retrospective cohort study; not stated; Scotland	1,701	Median 74 years	60	Participants with type 2 diabetes and incident chronic heart failure
Luk 2013 (12)	Prospective cohort study; July 1994–2009; Hong Kong	8,439 No CKD at baseline: 7,184 No CVD at baseline: 6,983	58 years	47	Participants in the Hong Kong Diabetes Registry Patients with baseline CKD were excluded in the analysis of the renal end point, and patients with baseline CVD were excluded in the analysis of cardiovascular end points
Ma 2012 (15)	Retrospective cohort study; 2003–2010; Taiwan	881	60 years	48	Participants in the Diabetes Shared Care Program at the Cardinal Tien Hospital and attending clinic approximately every 3 months
Penno 2013 (16,17)	Prospective cohort study; 2007–2008; Italy	8,260	Median 68 years	57	Participants included in the RIACE Italian Multicentre Study with HbA_{1c} values of 3–5% measured serially in a 2-year period
Rodríguez-Segade 2012 (26)	Prospective cohort study, March 1994–March 2009; Spain	2,103	59 years	48	Participants with diabetes attending outpatient clinics of the University Hospital Complex of Santiago de Compostela
Skriver 2015 (19)	Prospective cohort study; 1970–2010; Denmark	11,205	Median 64 years	52	Participants with type 2 diabetes with registered public data files in Aarhus County, Denmark, who subsequently had at least three HbA_{1c} measurements
Sugawara 2012 (27)	Prospective cohort study; 2000–2007; Japan	812	55 years	69	Participants with type 2 diabetes in the Tsukuba Kawai Diabetes Registry database
Takao 2014 (13)	Retrospective cohort study, 1995–2012; Japan	754	54 years	82	Participants with type 2 diabetes attending an outpatient clinic and followed up for 2 years with at least four HbA_{1c} levels

CKD, chronic kidney disease; CVD, cardiovascular disease; FinnDiane, Finnish Diabetic Nephropathy Study; RCT, randomized controlled trial; RIACE, Renal Insufficiency And Cardiovascular Events.

Table 2—Risk of bias among studies that evaluated glycemic variability and adverse outcomes

Study ID	Time frame and number of samples used to define HbA_{1c} variability	Case definition, ascertainment, and assessment frequency	<10% loss to follow-up	Adjustments for potential confounders
Studies of participants with type 1 diabetes				
Hermann 2014 (14)	Between 1990 and March 2013 Median number of HbA_{1c} values per patient during 1 year: 4.3	Diabetic retinopathy according to trained ophthalmologist direct fundoscopy in mydriasis to grade condition based on modified Airlie House Classification/ETDRS standards Frequency of evaluation unclear	Unclear	Age at diabetes diagnosis, sex, and median HbA_{1c}
Hietala 2013 (11)	Average follow-up: 5.2 years 10 (IQR 3–18) HbA_{1c} measurements per patient	Proliferative retinopathy from fundus photographs and/or records of dilated slit lamp fundus examination performed by an ophthalmologist Photographs taken for a median of 3 (IQR 1–5) occasions per patient Proliferative retinopathy defined as ≥61 on ETDRS grading scale	Unclear	Renal status, diabetes duration, mean HbA_{1c}, blood pressure, sex, and number of HbA_{1c} measurements
Kilpatrick 2008 (6)	Average follow-up: 6.5 years HbA_{1c} was measured quarterly but number of HbA_{1c} measurements per patient unclear	Development and progression of diabetic retinopathy defined as a change from baseline of ≥3 units on the ETDRS interim score on any two successive annual evaluations Nephropathy defined as an increase in AER ≥40 mg/24 h on any annual evaluation provided that baseline AER was <40 mg/dL	Unclear	Age, sex, disease duration, randomization treatment, prevention cohort, and baseline HbA_{1c}
Marcovecchio 2011 (29)	Between 1986 and 1996 and between 2000 and 2005 Median number of HbA_{1c} assessments: 4 (2–16)	Microalbuminuria was defined as ACR 3.5–35 mg/mmol in men and 4.0–47 mg/mmol in women in two of three consecutive early morning urine samples measured annually	Unclear	Sex, age at diagnosis, chronologic age, and mean HbA_{1c}
Nazim 2014 (35)	Follow-up: 9.2 years Number of HbA_{1c} measurements unclear	Microalbuminuria defined as AER ≥20 μg/min and <200 μg/min in at least two samples obtained within two or more samples obtained within a period of 3–6 months Frequency of urine testing unclear	Unclear	Age at onset of diabetes, presence of arterial hypertension at baseline, mean HbA_{1c}, and mean insulin daily dose
Raman 2011 (25)	Average follow-up: 7 years Number of HbA_{1c} measurements unclear	Microalbuminuria (AER ≥20 μg/min or microalbumin:creatinine ratio ≥30 mg/g) Frequency of urine testing unclear	Unclear	Age, sex, race, and mean HbA_{1c}

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Table 2—Continued

Study ID	Time frame and number of samples used to define HbA_{1c} variability	Case definition, ascertainment, and assessment frequency	<10% loss to follow-up	Adjustments for potential confounders
Wadén 2009 (10)	Median follow-up: 5.7 years Median number of HbA_{1c} measurements per patient: 13 (IQR 7–20), 2.13 measurements per patient per year	Renal status prospectively assessed by review of all recorded values of urine AER and medical records Progression of renal disease defined as a shift to a higher albuminuria level in any two (of three) consecutive urine collections or end-stage renal failure Cardiovascular events (myocardial infarction, coronary artery procedure, stroke, limb amputation due to ischemia, peripheral artery procedure) based on medical records at baseline and follow-up Frequency of evaluation unclear	Unclear	Duration of diabetes, sex, blood pressure, total cholesterol, smoking, intrapersonal mean of serial HbA_{1c} measurements, number of HbA_{1c} measurements, diabetic nephropathy, and baseline cardiovascular events
Studies of participants with type 2 diabetes				
Lin 2013 (28)	Average follow-up: 4.40 years Patients had to have more than two HbA_{1c} measurements each year Although not reported, patients likely had more than eight HbA_{1c} measurements	Diabetic nephropathy defined as eGFR <60 mL/min/1.73 m^2 and patients followed up regularly every 3–6 months	Yes	Age, sex, lifestyle factors, comorbidities, myocardial infarction, mean fasting plasma glucose, mean HbA_{1c}, and drug treatments
Cummings 2011 (23)	Average follow-up: 7.6 years Patients had to have at least five HbA_{1c} measurements	Increase of one or more CKD stages based on baseline and most recent follow-up visit	Unclear	Age, race, sex, duration of diabetes, blood pressure, drug treatments, initial HbA_{1c} and number of HbA_{1c} values, and fasting blood glucose CV
Foo 2014 (20)	Follow-up of 2 years with serial 3-monthly HbA_{1c} (range 3–6) values per patient	Moderate diabetic retinopathy or worse assessed using retinal photographs of both eyes with an ETDRS level ≥43 after 2 years of HbA_{1c} measurement	Unclear	Age, sex, ethnicity, duration of diabetes, hypertension, hyperlipidemia, smoking, microalbuminuria and cardiovascular events, and mean and SD of HbA_{1c}
Hirakawa 2014 (18)	Median study follow-up: 3 years Five HbA_{1c} measurements per patient	Composite outcomes of major macrovascular events (death from cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke), major microvascular events (new or worsening nephropathy or retinopathy) and all-cause mortality Patients followed up for first 24 months Frequency of evaluation unclear	Yes	Age, sex, randomized blood pressure lowering, region, duration of diabetes, smoking status, alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, BMI, medications, and mean HbA_{1c} or fasting glucose in the first 24 months

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Table 2—Continued

Study ID	Time frame and number of samples used to define HbA_{1c} variability	Case definition, ascertainment, and assessment frequency	<10% loss to follow-up	Adjustments for potential confounders
Hsu 2012 (24)	Average follow-up: 6.2 years Blood collected every 6 months but number of HbA_{1c} measurements per patient unclear	Microalbuminuria defined as ACR ≥3.4 mg/mmol in two consecutive urine tests Frequency of urine testing unclear	Yes	Age at diabetes onset, sex, education, diabetes duration, smoking status, waist circumference, serum lipids, mean HbA_{1c}, blood pressure, and ACE inhibitor or angiotensin receptor blocker use
Lang 2015 (36)	Median follow-up: 3.3 years Frequency of evaluation or number of HbA_{1c} measurements unclear	Method of mortality ascertainment unclear	Unclear	Significant covariates, including chronic heart failure duration and current drug exposure
Luk 2013 (12)	Median follow-up: 7.2 years Median HbA_{1c} measurements: 10 (IQR 5–17)	Incident CKD (eGFR <60 mL/min/1.73 m^2) and incident CVD (myocardial infarction, ischemic heart disease, peripheral vascular disease, heart failure, ischemic stroke) and end-stage renal disease obtained from Hospital Authority discharge diagnoses	Unclear	Age, sex, smoking history, diabetes duration, BMI, waist circumference, blood pressure, serum lipids, log urine ACR, eGFR, hemoglobin, and medication use
Ma 2012 (15)	Average follow-up: 4.7 years Average number of HbA_{1c} measurements: 12 ± 7	Mortality and cause of death obtained from computerized death certificates maintained by the Department of Health, Executive Yuan, Taiwan	Yes	Age, sex, BMI, duration of diabetes, blood pressure, use of antihypertensives and statins, mean LDL cholesterol, smoking status, CKD, and mean HbA_{1c} values
Penno 2013 (16,17)	Follow-up unclear Average number of HbA_{1c} measurements: 4.52 ± 0.76 Patients had to have three to five HbA_{1c} measurements	Diabetic nephropathy by albuminuria and eGFR with unclear frequency of evaluation Diabetic retinopathy assessed at baseline by dilated fundoscopy; follow-up evaluation unclear CVD (acute myocardial infarction; stroke; foot ulcer or gangrene; amputation; coronary, carotid, and lower-limb revascularization; and surgery for aortic aneurysm) assessed from medical records and adjudicated based on hospital discharge records of specialist visit by an ad hoc committee in each center	Yes	Age, BMI, sex, known disease duration, smoking habits, triglycerides, HDL cholesterol, hypertension, dyslipidemia, previous major CVD events, specific diabetes treatments, and eGFR and albuminuria categories if diabetic retinopathy was dependent variable or diabetic retinopathy categories if renal parameters were dependent variable
Rodríguez-Segade 2012 (26)	Average follow-up: 6.6 years Median number of HbA_{1c} measurements per patient: 10 (IQR 6–14)	Progression of diabetic nephropathy if AER ≥100 mg/24 h and had been <40 mg/24 h at entry or if AER ≥300 mg/24 h and had been <200 mg/24 h at entry Frequency of urine testing unclear	Unclear	Age, duration of diabetes, use of insulin, baseline HbA_{1c}, BMI, retinopathy status, use of antihypertensive agents, smoking status, lipid status, sex, cohort, number of HbA_{1c} measurements, and updated mean

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Table 2—Continued

Study ID	Time frame and number of samples used to define HbA_{1c} variability	Case definition, ascertainment, and assessment frequency	<10% loss to follow-up	Adjustments for potential confounders
Skriver 2015 (19)	Median follow-up: 6 years Number of HbA_{1c} measurements per patient was at least 3	All-cause mortality from record linkage with nationwide Danish Civil Registration System	Unclear	Age, sex, medications, prior CVD, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, hemiplegia, moderate to severe renal disease, diabetes with end-organ damage, any tumor, leukemia, lymphoma, moderate or severe liver disease, metastatic solid tumor, AIDS, and index HbA_{1c}
Sugawara 2012 (27)	Average follow-up: 4.3 years Median number of HbA_{1c} measurements per patient: 11 (5–12)	Microalbuminuria was defined as ACR ≥3.4 mg/mmol for at least two of three measurements During follow-up period, ACR was evaluated every 6 months	Yes	Age, sex, duration of diabetes, blood pressure, BMI, serum lipids, and smoking status
Takao 2014 (13)	Median follow-up: 15.9 years Median number of HbA_{1c} per patient: 79 (40–117)	Unclear method of mortality ascertainment and frequency of evaluation	No, 27.5% lost to follow-up	Age, sex, mean HbA_{1c}, number of HbA_{1c} measurements, duration of diabetes, BMI, blood pressure, serum lipids, and smoking status

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ETDRS, Early Treatment of Diabetic Retinopathy Study; IQR, interquartile range.

that adjusted for duration of diabetes, number of HbA_{1c} measurements, comorbidities, and baseline medications produced similar results to those recorded with inclusion of all studies (Supplementary Table 1).

Type 2 Diabetes

Studies reporting all-cause mortality as an outcome were not pooled due to high levels of heterogeneity, which was believed to be a result of differing follow-up durations and loss to follow-up. The outcome, therefore, was split according to short follow-up (<5 years) and long follow-up (≥5 years).

Six studies evaluated adverse outcomes by considering the impact of HbA_{1c} CV (13,15,18,26,28,36), and nine studies considered HbA_{1c} SD (12,13,15–18,20,24,26,27). Increase in HbA_{1c} variability defined by high versus low CV groups was associated with increased risk of diabetic nephropathy (RR [95% CI] 1.58 [1.19–2.10]) and all-cause mortality in studies with ≥5 years of follow-up (2.89 [1.45–5.74]) and in those with <5 years follow-up (1.06 [1.01–1.11]) (Supplementary Fig. 3*A*). Incremental increases in CV were also associated with a significantly increased risk of nephropathy (1.03 [1.01–1.05]), macro/microvascular events (1.11 [1.02–1.21]), macrovascular events (1.18 [1.04–1.33]), and mortality with ≥5 years of follow-up (1.10 [1.03–1.16]) and <5 years of follow-up (1.31 [1.16–1.48]). No significant association was found between incremental increase in CV and microvascular events (1.07 [0.96–1.20]) (Supplementary Fig. 3*B*).

Considering HbA_{1c} variability with SD, high versus low SD group was associated with increased risk of nephropathy (RR [95% CI] 1.24 [1.02–1.51]), all-cause mortality (2.34 [1.48–3.71], two studies), microalbuminuria (1.34 [1.15–1.57], two studies), macroalbuminuria (1.41 [1.03–1.93]), ulceration/gangrene (1.50 [1.06–2.12]), and mortality in studies with ≥5 years of follow-up (3.09 [1.45–6.58]) and in those with <5 years of follow-up (1.99 [1.11–3.55]) (Supplementary Fig. 4*A*). Incremental increase in SD was associated with an increased risk of nephropathy (1.22 [1.05–1.42], two studies), end-stage renal failure (1.53 [1.35–1.73]), microalbuminuria (1.20 [1.03–1.39]), macro/microvascular events (1.12

Table 3—Results of studies that evaluated glycemic variability and adverse outcomes

Study ID	Definition of glycemic variability	Outcomes evaluated	Study follow-up	Results
Studies of participants with type 1 diabetes				
Hermann 2014 (14)	HbA_{1c} CV	Diabetic retinopathy	1990–March 2013	Cox proportional hazards multiple regression for diabetic retinopathy with HbA_{1c} CV based on participants above or below the 50th centile (HR 1.11 [1.10–1.12]) HbA_{1c} variability led to an additional rise in risk (3.5% higher risk of diabetic retinopathy per 1-unit increase of HbA_{1c} CV at 10 years of diabetes duration
Hietala 2013 (11)	HbA_{1c} CV	Proliferative retinopathy	In cohort with no prior laser treatment, mean 5.2 ± 2.2 years Unclear in other cohort	Among participants with verified retinopathy status and indications for laser treatment, Fine and Gray regression model for risk of proliferative retinopathy according to quartiles of HbA_{1c} CV: First quartile: HR 1.00 (reference) Second quartile: HR 1.3 (0.97–1.8) Third quartile: HR 1.5 (1.1–2.0) Fourth quartile: HR 1.7 (1.3–2.2) Fine and Gray regression model for retinopathy among patients with no prior laser treatment requiring laser treatment by HbA_{1c} variability first quartile vs. fourth quartile (HR 1.6 [1.1–2.5])
Kilpatrick 2008 (6)	HbA_{1c} SD	Development and progression of diabetic retinopathy and nephropathy	6.5 years	Cox proportional hazards multiple regression of risk of retinopathy with HbA_{1c} SD (1% increase SD): HR 2.11 (1.54–2.89) Risk of nephropathy with HbA_{1c} SD (1% increase SD): HR 1.86 (1.41–2.47)
Marcovecchio 2011 (29)	HbA_{1c} SD	Microalbuminuria	Unclear	Cox proportional hazards multiple regression for risk of development of microalbuminuria by HbA_{1c} SD (for every 1-unit increase in each covariate): HR 1.31 (1.01–1.35)
Nazim 2014 (35)	HbA_{1c} CV	Microalbuminuria	9.2 ± 3.4 years	Cox proportional hazards multiple regression for risk of developing first episode of microalbuminuria by HbA_{1c} CV (per unit increase): HR 1.04 (1.00–1.08)
Raman 2011 (25)	HbA_{1c} SD	Microalbuminuria	7.00 ± 2.85 years	Cox proportional hazards multiple regression for microalbuminuria by HbA_{1c} SD (per unit increase): HR 1.91 (1.37–2.66)
Wadén 2009 (10)	HbA_{1c} SD	Cardiovascular event and progression in renal status (higher albuminuria level in any two of three consecutive urine collections or to end-stage renal disease)	Median follow-up: 5.7 years	Cox proportional hazards multiple regression for risk of progression in renal status by HbA_{1c} SD (defined according to quartiles of HbA_{1c} SD): HR 1.92 (1.49–2.47) Risk of cardiovascular event by HbA_{1c} SD (defined according to quartiles of HbA_{1c} SD): HR 1.98 (1.39–2.82)

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Table 3—Continued

Study ID	Definition of glycemic variability	Outcomes evaluated	Study follow-up	Results
Studies of participants with type 2 diabetes				
Lin 2013 (28)	HbA_{1c} CV	Diabetic nephropathy	4.40 years	Cox proportional hazards multiple regression for diabetic nephropathy with HbA_{1c} CV <6.68 (HR 1.00 [reference]), 6.68–13.4 (HR 1.18 [0.88–1.58]), and >13.4 (HR 1.58 [1.19–2.11])
Cummings 2011 (23)	Average excess of HbA_{1c} >7%	Increase of one or more CKD stages	7.6 ± 1.9 years	Multiple logistic regression model of worsening by one or more CKD stages with average excess of HbA_{1c} >7% (OR 1.173 [1.031–1.335])
Foo 2014 (20)	HbA_{1c} SD	Moderate diabetic retinopathy	2 years	Multivariable logistic regression for moderate diabetic retinopathy with HbA_{1c} SD (adjusted OR 1.49 [0.72–3.07])
Hirakawa 2014 (18)	HbA_{1c} CV and SD	Composite of major macrovascular (death from cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular (new or worsening nephropathy or retinopathy) events Microvascular events Macrovascular events All-cause mortality	Median 3 years	Cox proportional hazards multiple regression models HbA_{1c} CV 1-SD increase and risk of outcomes: Macro/microvascular events: HR 1.11 (1.02–1.21) Major macrovascular events: HR 1.18 (1.05–1.34) Major microvascular events: HR 1.07 (0.96–1.2) All-cause mortality: HR 1.31 (1.16–1.48) Continuous HbA_{1c} SD 1-SD increase and risk of outcomes: Macro/microvascular events: HR 1.12 (1.02–1.22) Major macrovascular events: HR 1.21 (1.06–1.38) Major microvascular events: HR 1.08 (0.96–1.21) All-cause mortality: HR 1.34 (1.18–1.53)
Hsu 2012 (24)	HbA_{1c} SD	Development of microalbuminuria	6.2 years	Cox proportional hazards multiple regression for incidence of microalbuminuria with HbA_{1c} SD quartiles: Quartile 1: HR 1.00 (reference) Quartile 2: HR 1.03 (0.72–1.48) Quartile 3: HR 1.09 (0.75–1.57) Quartile 4: HR 1.48 (1.03–2.12)
Lang 2015 (36)	HbA_{1c} CV	All-cause mortality	Median follow-up: 3.3 (0.9–7.5) years	Cox proportional hazards multiple regression for mortality with 0.01 increase in CV: From 0.036 (Q1) to 0.046: adjusted HR 1.04 (1.02–1.07) From 0.064 (Q2) to 0.074: adjusted HR 1.03 (1.01–1.05) From 0.11 (Q3) to 0.12: adjusted HR 1.02 (1.01–1.03)

Continued on p. 2365

Table 3—Continued

Study ID	Definition of glycemic variability	Outcomes evaluated	Study follow-up	Results
Luk 2013 (12)	HbA_{1c} SD	Incident CKD (eGFR $<$60 mL/min/1.73 m^2), incident CVD (myocardial infarction, ischemic heart disease, peripheral vascular disease, heart failure, ischemic stroke), and end-stage renal disease	Median follow-up: 7.2 years	Cox proportional hazards multiple regression for risk of adverse outcome with adjusted HbA_{1c} SD: Incident CKD: HR 1.16 (1.10–1.22) End-stage renal failure: HR 1.53 (1.35–1.73) Incident CVD: HR 1.27 (1.15–1.40)
Ma 2012 (15)	HbA_{1c} SD and CV	All-cause mortality	4.7 $\pm$ 2.3 years	Cox proportional hazards multiple regression for risk of all-cause mortality with: HbA_{1c} SD ($>$50th centile vs. $<$50th centile): HR 1.99 (1.11–3.54) HbA_{1c} CV ($>$50th centile vs. $<$50th centile): HR 1.06 (1.01–1.11)
Penno 2013 (16,17)	HbA_{1c} SD	Diabetic nephropathy by albuminuria and eGFR Diabetic retinopathy CVD; acute myocardial infarction; stroke; foot ulcer or gangrene; amputation; coronary, carotid, and lower-limb revascularization; and surgery for aortic aneurysm	Unclear	Multiple logistic regression of outcomes by HbA_{1c} SD quartiles: Microalbuminuria Quartile 1: OR 1.00 (reference) Quartile 2: OR 1.03 (0.878–1.22) Quartile 3: OR 1.14 (0.968–1.35) Quartile 4: OR 1.31 (1.10–1.56) Macroalbuminuria Quartile 1: OR 1.00 (reference) Quartile 2: OR 0.939 (0.672–1.31) Quartile 3: OR 1.04 (0.757–1.44) Quartile 4: OR 1.41 (1.03–1.93) eGFR $<$60 mL/min/1.73 m^2 Quartile 1: OR 1.00 (reference) Quartile 2: OR 1.00 (0.838–1.20) Quartile 3: OR 1.23 (1.03–1.48) Quartile 4: OR 1.24 (1.02–1.51) Multiple logistic regression 1% increment of HbA_{1c} SD nonadvanced diabetic retinopathy vs. no retinopathy: OR 0.917 (0.758–1.11) Multiple logistic regression of HbA_{1c} SD quartiles and ulceration/gangrene: Quartile 1: OR 1 (reference) Quartile 2: OR 1.06 (0.736–1.52) Quartile 3: OR 1.02 (0.709–1.46) Quartile 4: OR 1.50 (1.06–2.12)
Rodríguez-Segade 2012 (26)	HbA_{1c} SD and CV	Progression of diabetic nephropathy; if AER $\geq$100 mg/24 h and had been $<$40 mg/24 h at entry, or if AER $\geq$300 mg/24 h and had been $<$200 mg/24 h at entry	6.6 years	Cox proportional hazards multiple regression for risk of progression of nephropathy by: HbA_{1c} SD (per 11 mmol/mol [1%] increase): HR 1.37 (1.12–1.69) HbA_{1c} CV: HR 1.03 (1.01–1.04)

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Table 3—Continued

Study ID	Definition of glycemic variability	Outcomes evaluated	Study follow-up	Results
Skriver 2015 (19)	Mean absolute residual around the line connecting index value and closing value	All-cause mortality	6 years	For index HbA_{1c} ≤8% (64 mmol/mol), variability >0.5 associated with increased mortality (HR 1.3 [1.1–1.5]) per HbA_{1c} percentage point variability For individuals with index HbA_{1c} >8% (64 mmol/mol), no association between HbA_{1c} variability and mortality was identified
Sugawara 2012 (27)	HbA_{1c} SD	Microalbuminuria	4.3 ± 2.7 years	Cox proportional hazards multiple regression for risk of microalbuminuria by incremental HbA_{1c} SD (per 1-SD increment): HR 1.20 (1.03–1.39)
Takao 2014 (13)	HbA_{1c} SD and CV	All-cause mortality	Median follow-up: 15.9 years	Cox proportional hazards multiple regression for risk of all-cause mortality with HbA_{1c} SD (HR 3.17 [1.43–7.03]) and HbA_{1c} CV (HR 1.10 [1.04–1.16]) Cox proportional hazards multiple regression models for all-cause mortality with HbA_{1c} SD tertiles: Tertile 1: HR 1 Tertile 2: HR 1.45 (0.730–2.88) Tertile 3: HR 3.09 (1.45–6.58) Cox proportional hazards multiple regression models for all-cause mortality, HbA_{1c} CV tertiles: Tertile 1: HR 1 Tertile 2: HR 1.21 (0.616–2.38) Tertile 3: HR 2.89 (1.45–5.74)

AER, albumin excretion rate; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

[1.02–1.22]), macrovascular events (1.21 [1.06–1.38]), cardiovascular disease (1.27 [1.15–1.40]), and mortality in studies with ≥5 years of follow-up (3.17 [1.43–7.03]) and in those with <5 years of follow-up (1.34 [1.18–1.53]). No significant association was found between incremental increase in SD and microvascular events (1.08 [0.96–1.21]) or retinopathy (1.03 [0.69–1.53], two studies) (Supplementary Fig. 4*B*).

A study by Penno et al. (17) reported additional nonsignificant associations with any lower-limb vascular event, any cerebrovascular event, any coronary event, acute myocardial infarction, any cardiovascular disease, and stroke. This study could not be included in the meta-analysis because raw data were not provided. Data on the significant association of HbA_{1c} CV and all-cause mortality reported by Lang et al. (36) (RR [95% CI] 1.02 [1.01–1.03]) were not included in the meta-analysis because all participants had incident chronic heart failure, increasing heterogeneity with other studies and affecting external validity.

Cummings et al. (23) reported a significant worsening of one more chronic kidney disease stages with an average excess HbA_{1c} >7% (53 mmol/mol) (OR 1.173 [95% CI 1.031–1.335]). Hirakawa et al. (18) also used other variability measures, including HbA_{1c} variation independent of the mean, HbA_{1c} residual SD, and HbA_{1c} average real variability. All were significantly associated with macrovascular complications, macro/microvascular complications, and mortality based on data from ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) (hazard ratio [HR] [95% CI]: variation independent of the mean HbA_{1c} 1.17 [1.04–1.32], 1.11 [1.02–1.2], 1.30 [1.15–1.46]; residual SD HbA_{1c} 1.20 [1.07–1.35], 1.10 [1.01–1.19], 1.33 [1.19–1.49]; average real variability HbA_{1c} 1.21 [1.07–1.37], 1.11 [1.02–1.21], 1.38 [1.22–1.55]). Skriver et al. (19) defined HbA_{1c} variability as the mean absolute residual around the line connecting index value and closing value. They reported that for index HbA_{1c} ≤8% (64 mmol/mol), variability >0.5 was associated with increased all-cause mortality (HR 1.3 [95% CI 1.1–1.5]) per HbA_{1c} percentage point variability. However, for individuals with

index HbA_{1c} >8% (64 mmol/mol), no association between HbA_{1c} variability and mortality could be identified.

Sensitivity analyses for study type and studies that adjusted for duration of diabetes, number of HbA_{1c} measurements, baseline medications, and comorbidities produced similar results to those that included all studies (Supplementary Table 2). There were too few studies in the meta-analysis to assess publication bias.

CONCLUSIONS

Glycemic variability is emerging as a measure of glycemic control that may be an important predictor of complications in patients with diabetes. Our analysis suggests that greater HbA_{1c} variability, irrespective of the definition used, is associated with adverse outcomes in several micro- and macrovascular end points and mortality. We report that HbA_{1c} variability in type 1 and type 2 diabetes is associated with renal and cardiovascular disease. The former is supported by 10 studies using both CV and SD as a measure of HbA_{1c} variability (6,10,12,16,24–29). Only one small cross-sectional study in a pediatric cohort using CV did not report this significant association (35). The latter is supported by two studies using SD (10,12). Retinopathy appears to be associated with HbA_{1c} variability in type 1 diabetes (6) but not in type 2 diabetes (16,20). However, this was shown with SD as the measure of variability (6) and not with CV (11,14). Four studies addressed the relationship with mortality in type 2 diabetes (13,15,18,19), with significant associations reported for SD and CV (13,15,18). Post hoc analysis of the ADVANCE data set showed HbA_{1c} variability defined by CV and SD to be associated with macrovascular events and combined macro/microvascular events but not with microvascular events in type 2 diabetes (18). These findings were independent of mean HbA_{1c}, suggesting that HbA_{1c} variability may be a useful additional risk stratification tool in both type 1 and type 2 diabetes.

The present results add to the findings of a significant association between HbA_{1c} SD and renal disease reported in the 2014 systematic review and meta-analysis by Cheng et al. (9). This meta-analysis of eight articles assessing the relationship between HbA_{1c} variability and renal disease in type 1 and type 2 diabetes has several limitations. Studies were excluded that did not report HR [including the study by Penno et al. (16)], measures of variability other than SD or CV were not considered, and different renal outcomes/end points were pooled.

The present results also differ from the previous systematic reviews of short-term glycemic variability and the risk of complications in diabetes (21,22). In previous studies, short-term glycemic variability was assessed by a variety of methods, such as SD, CV, and mean amplitude of glycemic excursions of daily glucose readings, including self-monitoring of blood glucose, continuous blood glucose monitoring, fasting plasma glucose, and postprandial glucose (21). These studies found no consistent evidence of a relationship between short-term glycemic variability and the risk of any complications in type 1 diabetes. However, in six studies involving patients with type 2 diabetes, both previous reviews found a positive association between glucose variability and retinopathy. In general agreement with these two reviews, we found a positive relationship between glycemic variability and cardiovascular disease in type 2 diabetes. The present finding of a significant association between HbA_{1c} variability and all-cause mortality in type 2 diabetes is consistent with the findings of Nalysnyk et al. (22) but not those of Smith-Palmer et al. (21).

These differing risk prediction results for short- and long-term glycemic variability may indicate differing pathological mechanisms. Short-term glycemic variability has been postulated to induce oxidative stress, inflammatory cytokines, and endothelial damage (37–41), mechanisms linked to diabetes complications (42,43). Additional mechanisms that may explain the association of HbA_{1c} variability and adverse events include cellular metabolic memory (44–47), insulin resistance (10,48), sensitivity of HbA_{1c} for detecting glycemic variability (44), and the exponential relationship between HbA_{1c} and risk of microvascular complications (16,44).

Confounding factors rather than a causal relationship may explain the association of HbA_{1c} variability with complications. These include poor medication compliance and self-management (10,12,28); multimorbidity (28); certain medications, such as steroids and antipsychotics (49); poor quality of life and lack of support (50,51); and infections (10).

Eight studies indicated that HbA_{1c} variability was superior at predicting diabetes-related complications than mean HbA_{1c} (6,10,12,13,15,17,24,25). Only one study found a significant association of mean HbA_{1c} with diabetes-related complications but not with HbA_{1c} variability (16,17). Further research is required to assess whether HbA_{1c} variability might be clinically useful for risk stratification and whether it might be a valuable therapeutic target.

To our knowledge, this systematic review and meta-analysis is the first of HbA_{1c} variability in diabetes and risk of mortality and complications other than renal disease. Limitations of the analysis are exclusion of non-English-language articles and studies before 2004. However, inclusion of studies earlier than the past 10 years may not be generalizable to current practices because current therapies (long-acting insulins, GLP-1 agonists, and dipeptidyl peptidase-4 inhibitors) were not available before 2004. Because of the small number of available studies, we were unable to use meta-regression to assess study characteristics as moderators. The heterogeneity estimates vary from very high to zero, and arguably, highly heterogeneous studies should not be meta-analyzed in the first place. However, homogeneity has been shown to be rare and often falsely assumed, especially for small meta-analyses, sometimes leading to false conclusions (52). From a statistical point of view, it is better to identify heterogeneity (which is likely present anyway), which can then be successfully accounted for in a random-effects meta-analysis model (53). Some limitations are inherent to the available literature, including the observational nature of studies, retrospective design of some, unclear or short follow-up periods, exclusion of patients deemed as having too few HbA_{1c} measurements (13,14,16,17,23,28), and the nonadjustment for different numbers of HbA_{1c} measurements, duration of diabetes, comorbidities, and baseline medications. In addition, there is no accepted method of assessing HbA_{1c} variability, and a single definition of outcomes was not used.

The present findings support the need for further studies investigating

the relationship between HbA_{1c} variability and diabetes complications. More-sophisticated measures of HbA_{1c} variability are needed as well as consensus about how such variability should be defined, including adjustment for differing intervals between HbA_{1c} measurements and addressing the temporality of the variance problem (54). The present findings suggest that HbA_{1c} variability may be a useful risk stratification tool in both type 1 and type 2 diabetes.

In conclusion, this meta-analysis shows significant associations between HbA_{1c} variability and all-cause mortality, renal disease, and cardiovascular disease in type 2 diabetes and retinopathy, renal disease, and cardiovascular disease in type 1 diabetes. These relationships are independent of mean HbA_{1c}, and in the majority of studies, variability was more predictive of adverse outcomes than mean HbA_{1c}.

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